1. **Priority Claim**

The Examiner has pointed out that the U.S. Patent No. listed in the Utility Patent Application Transmittal Sheet for the subject Application contained an incorrect Patent Number. The U.S. Patent No. for the priority claim inserted as the first sentence of the specification has been corrected from 5,521,003 to 5,521,303.

2. **Rejection of Claim 12 under 35 U.S.C. § 102 (b)**

The Examiner has rejected Claim 12 as being anticipated by Howard (US 3,846,541), stating that HOWARD discloses combination drug therapy, comprising ethyl-p-chlorophenoxyisobutyrate or the acid and (1) DEAE Sephadex, (2) cholestyramine, or (3) cholestipol to reduce serum cholesterol in humand with hyperlipidemia. The Examiner pointed specifically to Tables I and II and Tests 1 and 2 in HOWARD.

While not necessarily in agreement with the rejections made by the Examiner, Applicants have amended Claim 12 to expedite review and allowance, while reserving the right to prosecute the canceled subject matter in later applications.

Applicants have amended Claim 12 to recite sulfated polysaccharides having less than about 5.0 wt percent of sulfated polysaccharides having a molecular weight less than 75,000 Daltons and containing less than 0.5 weight percent of inorganic sulfate. Since sulfated polysaccharides having this molecular weight are not ethyl-p-chlorophenoxyisobutyrate or the acid, Applicants believe that the Examiner's rejection of Claim 12 has been overcome.

3. **Rejection of Claims 12-14 under 35 U.S.C. § 102 (b)**

The Examiner has rejected Claims 12-14 as being anticipated by EAST et al (Annual Inst. Med, 1988), stating that EAST discloses combination drug therapy, comprising lovastatin and gemfibrozil, to reduce serum cholesterol in humans with hyperlipidemia. The Examiner specifically pointed out page 25, left-hand column and Tables 2 and 3.

While not necessarily in agreement with the rejections made by the Examiner, Applicants have amended Claim 12 to expedite review and allowance, while reserving the right to prosecute the canceled subject matter in later applications.

Applicants have amended Claim 12 to recite sulfated polysaccharides having less than about 5.0 wt percent of sulfated polysaccharides having a molecular weight less than 75,000 Daltons and containing less than 0.5 weight percent of inorganic sulfate. Since sulfated polysaccharides having this molecular weight are not gemfibrozil, Applicants believe that the Examiner's rejection of Claim 12 has been overcome.

Claims 13 and 14 are dependent, directly or indirectly, on Claim 12. As such these dependent claims contain all of the limitations of the independent claim. For this reason Applicants believe that the Examiner's rejection of Claims 13 and 14 has been overcome.

4. **Rejection of Claims 12 and 15 under 35 U.S.C. § 103 (a)**

The Examiner has rejected Claims 12 and 15 as being unpatentable over KRAUSE (US 4,859,703), stating that the claims are drawn to a method for lowering serum cholesterol in humans comprising administration of a first compound that reduces serum cholesterol and a second compound that reduces serum cholesterol, wherein the second compound is an ACAT inhibitor. The Examiner points out that KRAUSE teaches a single dose combination of one of a number of hypocholestemic agents and an ACAT inhibitor. The Examiner further points out that KRAUSE does not specifically exemplify the administration of the compositions to humans to lower serum cholesterol. Finally, the Examiner states that it would have been obvious to one having ordinary skill in the art at the time the invention was made to administer the composition, comprising an ACAT inhibitor and another hypocholestemic agent. The Examiner states that the ordinarily skilled practitioner would be motivated to achieve a lowering of serum cholesterol with a reasonable expectation of success.

Applicants respectfully point out that Claim 12 recites sulfated polysaccharides with a given molecular weight. KRAUSE does not teach sulfated compounds as compounds to lower serum cholesterol. In addition, KRAUSE does not teach sulfated polysaccharides having less than about 5.0 wt percent of sulfated polysaccharides having a molecular weight less than 75,000 Daltons and containing less than 0.5 weight percent of inorganic sulfate.

Applicants also respectfully point out that there is nothing in KRAUSE that would motivate a person of ordinary skill to go from KRAUSE to the sulfated polysaccharides

of the present application and expect to have a reasonable expectation of success. KRAUSE teaches gemfibrozil, clofibrate, benafibrate, and fenofibrate as the first compound in a combination. If one looks at the compounds listed in KRAUSE one will see that they are all fibric acid derivatives. Fibric acid derivatives are not sulfated polysaccharides. Applicants respectfully point out that there is no motivation in KRAUSE to go from fibric acid derivatives to sulfated polysaccharides. There is no teaching in KRAUSE that would lead a person from KRAUSE to the compounds of the present invention. Also, since the KRAUSE compounds are very different from the compounds of the present invention, there is no reasonable expectation of success in going from fibric acid derivatives to sulfated polysaccharides.

The Examiner has also rejected Claim 15 as being obvious in view of KRAUSE. Claim 15 is dependent on Claim 12. This dependent claim contains all of the limitations of the independent claim.

For these reasons, Applicants respectfully request the Examiner to reconsider the obviousness rejection of Claims 12 and 15.

5. **Rejection of Claims 12-16 under 35 U.S.C. § 103 (a)**

The Examiner rejected claims 12-16 as being unpatentable over LANGE, stating that LANGE teaches the administration of sulfated polysaccharides which act as inhibitors of human cholesterol esterase to lower serum cholesterol. The Examiner points out the abstract, page 5 and example 4 of LANGE, and states that the reference further suggests the use of said polysaccharides in combination with other agents having cholesterol lowering activity. Particular agents pointed out by the Examiner are ACAT inhibitors (page 14, lines 19-25) and lovastatin (page 15, lines 21-24). The Examiner further points out that the use of the polysaccharides in combination with other agents is not specifically exemplified. In addition, the Examiner states that it would have been obvious to one having ordinary skill in the art at the time the invention was made to have used the disclosed inhibitors of human cholesterol esterase, the sulfated polysaccharides taught in LANGE in combination with other agents, such as ACAT inhibitors or lovastatin. Further, the Examiner states that the ordinarily skilled practitioner would have been motivated to obtain the combined effect of the agents in lowering serum cholesterol with a reasonable expectation of success.

Applicants respectfully point out that although LANGE teaches very large sulfated polysaccharides of molecular weight greater than 100,000 (see page 9, lines 21-23), LANGE does not teach the need for purified sulfated polysaccharides. On page 9, lines 1-5, of the subject application Applicants teach that the presence of free sulfate and low molecular weight sulfated polysaccharides are undesirable, even toxic. The presence of these impurities makes high molecular weight sulfated polysaccharides unsuitable for human pharmaceutical use. Claim 12 of the present invention contains limitations on the presence of both inorganic sulfate and low molecular weight sulfated polysaccharides.

Applicants further point out that since LANGE did not recognize that purified sulfated polysaccharides containing less than 5 weight percent of sulfated polysaccharides having a molecular weight less than 75,000 Daltons and containing less than 0.5 weight percent of inorganic sulfate are necessary for human pharmaceutical use, there is no motivation in LANGE to prepare the purified sulfated polysaccharides of the present invention.

The Examiner has also rejected dependent Claims 13-16. Applicants respectfully point out that Claims 13-16 are dependent claims that are subject to all of the limitations of independent Claim 12.

For the above reasons, Applicants ask that the Examiner reconsider the rejection of Claims 12-16 in view of LANGE.

Applicants request the Examiner to reconsider the rejections in view of the above arguments and claim amendments. Favorable reconsideration and allowance of the pending application claims is therefore courteously solicited.

Respectfully submitted,

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12. [Once Amended] A method for lowering serum cholesterol in humans comprising administering to a human the combination of ~~a first compound that reduces serum cholesterol levels~~ an essentially non-absorbable very high molecular weight sulfated polysaccharide having less than about 5.0 wt. percent of sulfated polysaccharides having a molecular weight less than 75,000 Daltons and containing less than 0.5 weight percent of inorganic sulfate and a second compound that reduces serum cholesterol levels.

13. The method of claim 12 wherein the second compound is at least one cholesterol synthesis blocker.

14. The method of claim 13 wherein the cholesterol synthesis blocker is lovastatin.

15. The method of claim 12 wherein the second compound is an inhibitor of ACAT.

16. The method of claim 12 wherein the sulfated polysaccharide is sulfated cellulose.

17. [New] A method for lowering serum cholesterol in humans comprising administering to a human the combination of an essentially non-absorbable very high molecular weight sulfated cellulose having less than about 5.0 wt. percent of sulfated cellulose having a molecular weight less than 75,000 Daltons and containing less than 0.5 weight percent of inorganic sulfate and lovastatin.

12. A method for lowering serum cholesterol in humans comprising administering to a human the combination of an essentially non-absorbable very high molecular weight sulfated polysaccharide having less than about 5.0 wt. percent of sulfated polysaccharides having a molecular weight less than 75,000 Daltons and containing less than 0.5 weight percent of inorganic sulfate and a second compound that reduces serum cholesterol levels.

13. The method of claim 12 wherein the second compound is at least one cholesterol synthesis blocker.

14. The method of claim 13 wherein the cholesterol synthesis blocker is lovastatin.

15. The method of claim 12 wherein the second compound is an inhibitor of ACAT.

16. The method of claim 12 wherein the sulfated polysaccharide is sulfated cellulose.

17. A method for lowering serum cholesterol in humans comprising administering to a human the combination of an essentially non-absorbable very high molecular weight sulfated cellulose having less than about 5.0 wt. percent of sulfated cellulose having a molecular weight less than 75,000 Daltons and containing less than 0.5 weight percent of inorganic sulfate and lovastatin.